Annals of Clinical and Analytical Medicine
Case Report

Restrictive factors for detection of responsible agent in perioperative anaphylaxis: A case report

Hacı Yusuf Güneş[1], Abdulmenap Güzel[2]
[1]Private Akdamar Hospital, Department of Anaesthesiology and Reanimation, Van
[2]Department of Anaesthesiology and Reanimation, Dicle University, Diyarbakir, Turkey

Abstract

Perioperative anaphylaxis is a type I hypersensitivity reaction, which rapidly develops with severe and variable clinical findings and can be fatal even in previously healthy patients. Early diagnosis and appropriate treatment are required but identifying the responsible agent is difficult. After anaphylaxis developed in our case, we did not have a healthy and adequate knowledge about the following questions. When should we get the blood sample, how much blood and to which tubes? Which tests can we work for detection of the responsible agent, where and in which laboratories? When we were communicating with the centers and laboratories which are given as references, we could not reach to standard information. Therefore, when perioperative anaphylaxis develops, it would be beneficial to have a set of perioperative anaphylaxis management guideline, including contact information of a national center for feedback and a reference anesthetic allergy testing center that could identify the responsible agent.

Keywords

General Anesthesia; Diagnostic Tests; Anaphylaxis; Perioperative Period

DOI:10.4328/ACAM.6005 Received: 17.08.2018 Accepted: 24.09.2018 Publihed Online: 25.09.2018 Printed: 01.07.2019 Ann Clin Anal Med 2019;10(4): 517-21
Corresponding Author: Abdulmenap Güzel, Department of Anesthesiology, Faculty of Medicine, Dicle University, Diyarbakır, Turkey.
T.: +90 4122488001/4328 GSM: +905052165597 F.: +90 4122488440 E-Mail: dr.amenap@gmail.com
ORCID ID: 0000-0003-2261-0072

Introduction

Anaphylaxis is an immunoglobulin E (IgE) mediated type I hypersensitivity reaction, which occurs with the release of primary mediators from basophils and mast cells into the circulatory system. Anaphylaxis is a type of vasogenic shock that can be life threatening, and is accompanied by a series of symptoms and findings ranging from mild acute respiratory distress to circulatory shock and collapse. Perioperative anaphylaxis is a clinical condition involving multiple organ systems that usually develops in response to anesthetic drugs or medical materials used in surgery [1–3]. Anaphylaxis may also occur during primary exposure due to cross-reactivity between many commercial products and drugs [4]. True anaphylaxis associated with anesthetic agents is rare, with anaphylactoid reactions being much more common. Muscle relaxants are the most common cause of anaphylaxis during anesthesia [2]. The clinical manifestations according to the Clinical Severity Scale of Immediate Hypersensitivity Reactions adapted from Ring and Messmer vary widely, from skin manifestations including erythema, edema, pruritus, and angioedema to the involvement of multiple organ systems and cardiac arrest [3]. When anaphylaxis occurs, allergy and immunological evaluations are important to identify the responsible agent and prevent relapse. Because there are no strategies for prophylactic treatment [3], early diagnosis and proper treatment management are the first two steps to achieving a successful outcome [4].

Here, we describe our experience regarding restrictive factors in the detection of the responsible agent and our clinical practices.

Case Report

A 28-year-old male patient weighting 85 kg with acute appendicitis was hospitalized for an emergency appendectomy. There were no food or drug allergies in his history. He reported only sun allergy in the summer months. Physical examination revealed no unusual features other than pain in the right lower quadrant. Findings consistent with acute appendicitis were obtained on the abdominal ultrasound. There were no abnormal findings on routine laboratory tests other than a C-reactive protein (CRP) level of 36 mg dL^{-1}. The patient, who had no previous history of illness, was the American Society of Anesthesiologists' physical status 1E. The antecubital vein was cannulated with an 18 G cannula for crystalloid infusion and an emergency appendectomy was planned under general anesthesia. After receiving written and verbal informed consent of the patient, premedication of midazolam (0.02 mg $kg)^{-1}$ was given. Routine monitoring showed a pulse rate of 80 beats per minute, noninvasive blood pressure of 110/70 mmHg, and peripheral capillary oxygen saturation (SpO_2) of 98. After induction with 2 µg kg^{-1} fentanyl, 3 mg kg^{-1} propofol, and 0.5 mg kg^{-1} rocuronium, endotracheal intubation was performed using a size 7.5 spiral cuffed tube. A mixture consisting of 50% O_2 + 50% N_2O + 2% sevoflurane was used for maintenance of anesthesia.

Within 2–3 min after induction, while surgical skin preparation was being performed using povidone iodine and the patient was being covered with sterile surgical covers; urticarial eruptions were noted on the upper side of the neck and chest with erythema and edema on the face. There was a slight increase in airway pressure and a decrease in SpO_2 to 87–90. As this was thought to indicate an allergic reaction, the patient was immediately given 100% oxygen while other anesthetic gases were stopped. Prednisolone (75 mg) was given intravenously. When hypotension (80/45 mmHg) and arrhythmia began to develop, adrenaline was administered at a dose of 0.2 mg intravenously, and the fluid replacement rate was increased. For arrhythmia, lidocaine hydrochloride 100 mg (Aritmal 2% ampoule) was administered intravenously. The cutaneous signs were mild but persisted. Therefore, dexamethasone 8 mg (Dekort amp 4 mg/mL; Deva, Istanbul, Turkey), the antihistaminic H_1 antagonist pheniramine maleate 45.5 mg (Avil amp; Sandoz, Istanbul, Turkey), and the H_2 antagonist ranitidine hydrochloride 50 mg (Ulcuran ampoule) were administered intravenously. The patient's blood pressure, arrhythmia, and oxygenation began to improve, and the erythema on the face decreased. The urticarial eruptions on the neck and upper chest lessened (Figures 1–2).

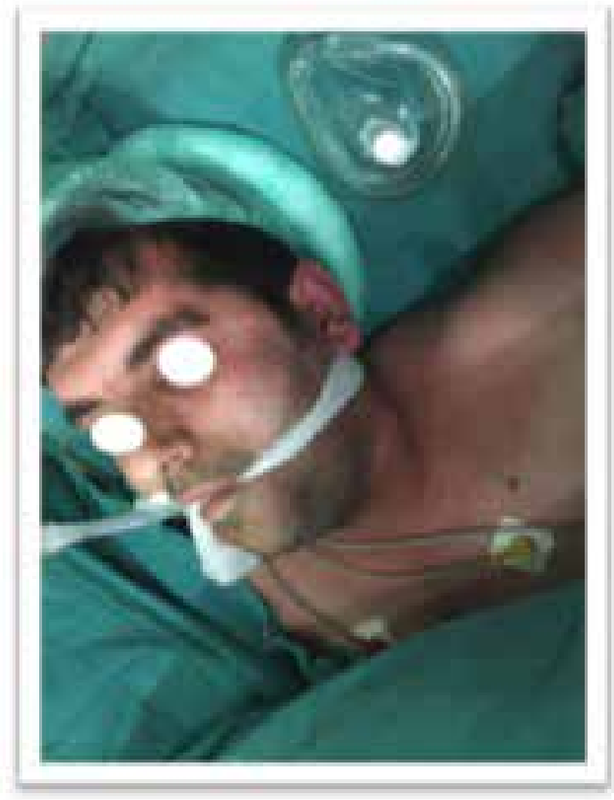

Figure 1. Erythema, Urticarial Eruptions and Edema on the face and ears of the patient.

Examination of the events after the patient's clinical condition had improved suggested that the patient may have suffered from anaphylaxis. Surgery was allowed to continue because of the urgent nature of the case and because the clinical findings of the patient improved after the emergency treatment. A blood sample was taken for detection of the responsible agent. We did not encounter other problems during the intraoperative period. Neuromuscular block was antagonized with 100 mg of sugammadex sodium (Bridion 200 mg/2 mL) after surgery without an additional dose, and the patient was awakened and extubated smoothly. The patient was monitored closely in the postoperative period but no problems occurred. The patient's relatives were informed of the incident. The next day, the patient was discharged with allergy-immunology polyclinic referral for further examination and differential diagnosis.

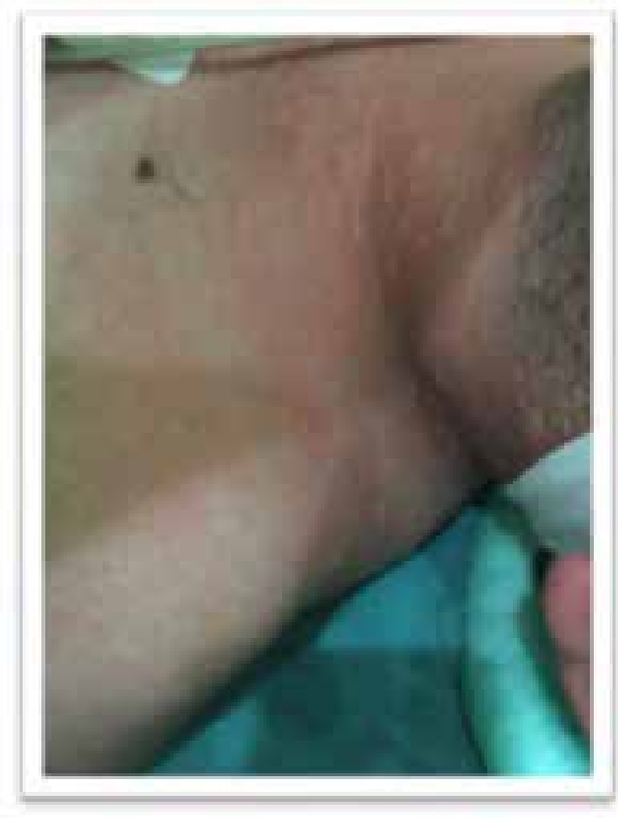

Figure 2. Erythema and Urticarial Eruptions on the upper part of neck and chest of the patient.

Discussion

Perioperative anaphylaxis is an important cause of anesthesia-related mortality and morbidity. The actual incidence is unknown and it is a rare event, although possibly underreported. All medicines and medical materials can cause allergic reactions in patients in the perioperative period [5]. It is difficult to estimate the worldwide rate of allergic reactions during anesthesia, but the reported rates are 1:35,006 in Canada, 1:60,002 in Norway, 1:10,000 to 1:200,007 in Australia, and 1:340,008 in the United States. Anaphylaxis reportedly has a mortality rate of 3.5–10% depending on the source of the data [6].

Anaphylaxis during anesthesia can lead to life-threatening consequences if not diagnosed and treated in a timely manner. Perioperative anaphylaxis has a number of unique aspects. Early signs and mild symptoms are not noticed, and skin signs are not visible or are noticed late because the patient is anesthetized or obscured under a surgical cover. The severity of anaphylaxis may be underestimated by anesthesiologists, and cardiovascular manifestations may initially be attributed to general anesthesia or central block. Therefore, when a severe anaphylaxis crisis is noticed, there is little time for treatment. As more than one drug is given to the patient in a short time during surgery, the responsible agent can only be estimated during the crisis. Allergenic agents are not limited to intravenous drugs or fluids, but also include other materials used in the operating room such as skin disinfectants, latex gloves, and catheters [6]. The three most common causes of perioperative anaphylaxis in patients under anesthesia are muscle relaxants (70%), latex (20%), and antibiotics 15%. Among the muscle relaxants, succinylcholine, atracurium, vecuronium, and pancuronium are the primary agents responsible for anaphylaxis. Anaphylaxis has also been reported for opioid drugs, but the incidence is extremely rare. Propofol is responsible for 1.2–2% of perioperative anaphylactic reactions. Isopropyl groups found in skin-care products can induce IgE sensitization with subsequent cross-reactivity with the isopropyl groups of the propofol molecule [6]. It is not a simple matter to define propofol as a triggering agent because perioperative anaphylaxis due to propofol hypersensitivity is so rare that the predictive capacities of individual tests and test combinations are not at the same level as for many other drugs. The intradermal test is thought to be more reliable than the skin prick test in diagnosing propofol allergy [7]. Since thiopental is rarely used these days, reports of reactions to it are very rare too. The incidence of thiopental allergy is 1: 30000. Ketamine allergy is very rare, and etomidate is considered the “most immunologically safe drug” in anesthesia. Anaphylaxis in response to benzodiazepines is extremely rare. There have been no reported anaphylactic reactions to any of the volatile anesthetics. Colloids used as volume expanders during surgery and trauma are responsible for 2.5% of all intraoperative anaphylactic reactions [6].

Povidone-iodine (betadine) is the most commonly used topical antiseptic solution in the surgery [8]. It may cause hypersensitivity associated with IgE by inducing histamine release. It can only affect the local area or whole body if it is widely applied [9].

The initial diagnosis of anaphylaxis relies on clinical grounds and should be followed by retrospective confirmation via skin testing and serology. The summary of the clinical severity scale of immediate hypersensitivity reactions during anesthesia is shown in Table 1 [6]. Early diagnosis and rapid treatment of anaphylaxis are very important to prevent adverse outcomes. Anaphylaxis should be considered if it is accompanied by skin findings, bronchospasm, or hypotension. The decision to continue or discontinue surgery is determined by the urgency of the surgery, the degree of anaphylaxis, and the underlying comorbidities of the patient [10].

Table 1. Severity Grades Of Allergic Reactions And Anaphylaxis During Anaesthesia [6].

Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous Erythema, Pruritus, Urticaria, Angioedema	Grade 1 signs plus Cardiovascular • Hypotension • Tachycardia • Presyncope Respiratory • Dyspnoea • Wheezing Gastrointestinal • Nausea • Vomiting • Diarrhea • Abdominal pain	Grade 2 signs plus Cardiovascular • Cardiovascular collapse • Profound hypotension • Bradycardia • Dysrhythmia Respiratory • Bronchospasm • Hypoxia(SaO2<92%) Gastrointestinal • Incontinence Neurologic • Confused • Unconscious	Cardiovascular • Pulseless electrical activity • Cardiac arrest

As a primer for perioperative anaphylaxis treatment (Table 2), it is necessary to stop the medication or serum, call for help, inform the surgeon, place the patient in the supine position as soon as possible, adopt the Trendelenburg position if hypotension is evident, take the airway under control and provide the patient with 100% oxygen. Adrenaline (epinephrine) is administered in mild to moderate anaphylaxis (Grades 1 and 2) as a 5–10 µg bolus, in severe anaphylaxis (Grades 3 and 4) as a 0.5–1 mg bolus or infusion of 0.05–1 µg kg^{-1} min^{-1} and 20 mL kg^{-1} bolus of crystalloid or colloid fluid treatment. Adequate fluid resuscitation with adrenaline (epinephrine) therapy is a critical step in the management of hypotension, as it has been shown that 35–70% of the blood volume may extravagate in 10–15 min [6,10].

Perioperative anaphylaxis can present as cardiac arrest, most commonly pulseless electrical activity. The Australian Resuscitation Council and the New Zealand Resuscitation Council recommendations for nonshockable rhythms are 1 mg adrenaline administered immediately and then repeated every 4 min. The 2015 recommendation from the American Heart Association is 1 mg adrenaline every 3–5 min. In secondary treatment, antihistamine (H_1 antagonist, promethazine 0.3–1 mg $kg;^{-1}$ H_2 antagonist, ranitidine 0.5–1 mg $kg)^{-1}$, corticosteroids (hydrocortisone 50 mg $kg)^{-1}$, and β_2 agonist nebulization (salbutamol 5–10 µg) are recommended [6,10]. We applied these treatments according to this protocol in our case.

Table 2. Management Of Perioperative Anaphylaxis [6]

Immediate Management	Dosage
Primary treatment	
• Stop administration of substance	
• Call for help, inform surgeon	
• Trendelenburg position	
• Airway management – oxygen	FiO_2 = 100%
Adrenalin (Dilute to 100 µg/ml)	
• Titrate to effect	Mild to moderate reaction (grade 1 or 2)
• Infusion (if large dose needed)	5-10 µg bolus Severe reaction (grade 3 or 4) 0,5-1 mg bolus 0,05-1 µg /kg/min
Fluid Therapy	
• Crystalloid or colloid	20ml/kg or more titrate to response
Secondary treatment	H1 antagonists: promethazine 0,3 -1 mg/kg
• Antihistamine	H2 antagonists: ranitidine 0,5-1 mg/kg
• Corticosteroids	Hydrocortisone 50mg/kg
• B2 agonists nebulisation	Salbutamol 5-10 µg

To detect the responsible agent when perioperative anaphylaxis develops, serum tryptase, histamine, and IgE levels should be investigated immediately and skin tests should be performed as later exposure can seriously increase the risk for mortality. Histamine is a preformed inflammatory mediator contained in granules of mast cells and basophils. An early increase in plasma histamine concentration indicates activation of mast cells and/or basophils, and is observed via allergic and nonallergic mechanisms; conversely, the absence of histamine increase does not preclude an immunological or non-immunological mechanism. The plasma half-life of histamine is assumed to be very short (15–20 min). Blood samples for histamine measurement should therefore be drawn within 30 min after a Grade I or II reactions, and within 2 h after severe reactions (Grades III and IV). The biological half-life of tryptase is about 2 h, with the peak level usually reached after 15–120 min from the start of the reaction. The level of tryptase decreases slowly in the following 3–6 h. The return to baseline can be measured 24 h after the reaction. Therefore, blood samples may be drawn within 15 and 60 min in Grade I or II reactions and within 30 min and 2 h in Grade III or IV reactions. The increase in serum tryptase is considered a reliable indicator of mast cell degranulation, and serum tryptase levels tend to be elevated in IgE-mediated and non-IgE mediated anaphylaxis. Tryptase concentrations may also increase in relation to late onset, biphasic anaphylaxis, or underlying mastocytosis. Serial measurements of serum tryptase are recommended, including the baseline value. In addition, histamine and tryptase concentrations are correlated with the severity of allergic reactions, and some groups have suggested that combined histamine and tryptase measurements should be performed for diagnosis of sudden reactions [3,10,11].

Specific IgE tests seem to be less sensitive than skin tests, and serum IgEs provide a possible explanation for the mechanism but do not confirm that the drug or agent was responsible for the reaction. Skin tests continue to be the gold standard for detection of IgE-mediated reactions. As premedication with antihistamine or corticosteroids does not prevent anaphylaxis, skin tests are helpful to identify the responsible agent and provide protection against future risks. Due to mast cell depletion, it should be done 4–6 weeks after the reaction to prevent false negative test results [3,10,11]. In our case, after vital signs had stabilized, a blood sample was taken to determine the responsible agent. However, we could not reach a reference anesthetic allergy testing center capable of identifying the responsible agent. The anaphylaxis reaction developed within 2–3 min after induction. There were no cutaneous signs on the povidone-iodine applied area and its surroundings. Therefore, we do not consider povidone-iodine as a responsible agent. Latex-induced anaphylaxis usually occurs for 30–60 min after surgery [3], so it is unlikely that latex was the responsible agent in our case, and we did not use antibiotics. One or more of the agents used for induction (fentanyl, propofol, and rocuronium) may have been the responsible agent. The use of sugammadex in the anaphylaxis following to administration of rocuronium is not recommended [10]. However, the neuromuscular block was successfully antagonized by sugammadex. Whole blood collected in a covered test tube was separated into blood cells and plasma by centrifugation, and serum was analyzed immediately. We considered these four agents as antigens and dropped two drops of each drug onto serum and whole blood samples to examine agglutination both macroscopically and microscopically. We observed both macroscopic and microscopic agglutination of serum and blood samples into which propofol was dropped. The findings obtained using both in vitro methods and the conventional method implies that propofol may have been the responsible agent in our case. However, this was not a definite diagnosis.

Conclusions

In conclusion, when perioperative anaphylaxis occurs, it would be beneficial to have a set of perioperative anaphylaxis man-

agement guidelines, including the contact information of a national center for feedback, and reference anesthetic allergy testing centers able to identify responsible agents. The feedback of data regarding these cases to a national center would make it easier to reach the correct conclusion and would prevent the repetition of anaphylactic events in the future.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Demirsoy S. Anaphylaxis. Turkiye Klinikleri. Journal of Pediatric Sciences. 2005; 1(9): 1-12.
2. Butterworth J, Mackey DC, Wasnick J. Anesthetic Complications. Morgan and Mikhail's Clinical Anesthesiology. 5th ed. Chapter 54. New York: McGraw-Hill Medical; 2013;1217-22
3. Dewachter P, Faivre CM, Charles W. Emala CW. Anaphylaxis and Anesthesia. Anesthesiology. 2009; 111(5): 1141-50
4. Ahmed A, Kumar A. Severe Anaphylactic Reaction at Induction of Anesthesia. J Pak Med Assoc. 2007; 57(9): 463-6.
5. Mota AC, Pereira F, Guimaraes J, Neves E, Sa P, Paiva M, et al. Propofol Induced Anaphylaxis-A Case Report. J Allergy Ther. 2015; 6: 209. DOI: 10.4172/2155-6121.1000209.
6. Dippennaar JM, Naidoo S. Allergic Reactions and Anaphylaxis During Anesthesia. Current Allergy and Clinical Immunology. 2015; 28(1): 18-22.
7. Harper NJH. Propofol and Food Allergy. British Journal of Anesthesia. 2016; 116 (1): 11–3. DOI:10.1093/bja/aev401.
8. Mali S. Anaphylaxis during the perioperative period. Anesthesia, Essays and Researches. 2012; 6(2): 124-33. DOI:10.4103/0259-1162.108286.
9. Altın F, Aydın S, Eygi B, Güneş T, Erkoç K, Kutas B, et al. An Allergic Reaction (Anaphylaxis) Observed Before Open Heart Surgeryin the Operating Room. Kosuyolu Heart J. 2013; 16(3). DOI: 10.5578/kkd.4720.
10. Kolawole H, Marshall SD, Crilly H, Kerridge R, Roessler P. Australian and New Zealand Anaesthetic Allergy Group/Australian and New Zealand College of Anaesthetists Perioperative Anaphylaxis Management Guidelines. Anaesth Intensive Care. 2017; 45(2): 151-8.
11. Meng J, Rotiroti G, Burdett E, Lukawska JJ. Anaphylaxis during general anaesthesia: experience from a drug allergy centre in the UK. Acta Anaesthesiologica Scandinavica. 2017; 61(3): 281-9. DOI: 10.1111/aas.12858.

How to cite this article:
Güneş HY, Güzel A. Restrictive factors for detection of responsible agent in perioperative anaphylaxis: a case report. J Clin Anal Med 2019;10(4): 517-21.